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Review

Genetics of type 2 diabetes in Arabs: What we know to date

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ABSTRACT

Type 2 diabetes (T2D) is among the most challenging health issues of the 21st century and is associated with an alarming rise in the incidence. The Arab population is no exception to this trend. The pathophysiological processes that lead to development of T2D are still unclear, however impairment in insulin secretion and/or action is clearly indicated. T2D is a complex disease with susceptibility being governed by the interaction of multiple genetic and environmental effects. Previous studies indicated that variants in genes encoding the pancreatic β-cell K+ATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) are associated with type 2 diabetes. The common Pro12Ala polymorphism in peroxisome proliferator-activated receptor-γ gene (PPAR-γ) was confirmed in several studies to be associated with type 2 diabetes as well. More recently, studies reported variants within a novel gene, TCF7L2, as a putative susceptibility gene for type 2 diabetes across many ethnic backgrounds around the world. However, studies to date in Arab cohorts remain limited.

The association of type 2 diabetes with the P12A polymorphism of the peroxisome proliferator-activated receptor gene (PPAR-γ) has been established in several populations [1]. While many variants have been identified in this gene, the most prevalent and best studied is the P12A polymorphism. There is considerable interpopulation variance in the incidence of the risk allele (P12). This ranges in frequency from a high of 0.96–0.98 in populations including the Japanese, Chinese, and African Americans to 0.91 in Pima Indians and a low of 0.81 in the Finnish population [2]. In the first Arab study of the P12A polymorphism of PPAR-γ, we observed the P, or risk allele, frequency to be 0.974 and 0.968 in type 2 diabetic and control subjects, respectively and was not statistically significant [3]. However, given the very high incidence of the P allele in this population, the study size was extremely underpowered. The high incidence of the P allele in the Saudi population was confirmed by a neonatal sample set in which frequency of this allele was found to be 0.957 [3]. Clearly the risk allele frequency of the Saudi population was comparable to the Japanese, Chinese, and African Americans and among the highest observed.

Insulin is secreted from pancreatic β-cells in response to nutrients, predominantly glucose but also fatty acids and some amino acids. Glucose metabolism is increased in response to rising cellular glucose levels and results in the production of ATP from ADP. Increased cytosolic ATP:ADP ratios trigger closure of KATP channels and membrane depolarization via reduced K+ efflux and subsequent activation of voltage gated calcium channels giving rise to transient increases in intracellular calcium. This in turn induces the exocytosis of insulin-containing granules [4]. Whilst voltage-gated and calcium-activated potassium channels are involved in membrane repolarisation, KATP channels transduce glucose-mediated metabolic signals into electrical activity which modulates insulin secretion. The KATP channel consists of two types of subunit: an inward-rectifier potassium channel subunit (Kir6.2) [5,6], and a sulfonylurea receptor subunit (SUR) [7]. The KATP channel is made of 4 Kir6.2 subunits coupled to four high-affinity SUR subunits [5,8–10]. The Kir6.2 subunit is encoded by KCNJ11, and the SUR subunit is encoded by ABCC8. Both genes reside adjacent to one another on chromosome 11. The four Kir6.2 subunits form the pore of the channel through which K+ passes and also contain the ATP-binding sites. The four SUR subunits modulate the activity of the channel and contain the binding site of sulfonylurea drugs [7]. Mutations in either KCNJ11 or ABBC8 can dramatically affect KATP channel activity, leading to either increased or decreased insulin release [11–15].

Common polymorphisms of ABCC8 and KCNJ11, particularly the E23K variant, have been associated with type 2 diabetes in several populations including non-European populations [16–26]. Current status of the E23K polymorphism and the implications for type 2 diabetes is discussed by Riedel et al. [27]. Direct effects of polymorphisms in ABCC8 (exon 16-3t/c, exon 18 C/T) have not been demonstrated, however, a functional role is proposed for the E23K variant of KCNJ11 which is reported to stimulate increased pancreatic β-cell activity, thus increasing the ATP threshold for insulin secretion [18]. The E23K variant of KCNJ11 results from a G → A

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transition in codon 23. Analysis of the E23K variant in several Caucasian populations showed that KK homozygosity had a stronger association with type 2 diabetes relative to EK heterozygosity or EE wild-type homozygosity [19]. We conducted the only study investigating an association between T2D risk and the E23K polymorphism of KCNJ11 in an Arab population to date. Our study confirmed in the Saudi population, association of the E23K allele with type 2 diabetes as seen in several other populations [16–26]. Whilst association with the K allele was evident, sample size did not establish whether the risk was recessive in nature and driven by the KK genotype. Other studies have indicated that association could be driven by KK homozygosity [22], however even with the high consanguinity rate in the Saudi population (~60%) [28] where recessive effects are likely to be amplified, this was not readily evident.

Researchers at Decode Genetics reported strong association between variants in a novel susceptibility gene called TCF7L2 and type 2 diabetes in Icelandic diabetic patients [29]. TCF7L2 encodes the transcription factor 7-like 2 [30]. The overexpression of this gene in human pancreatic β-cells was shown to associate with impaired insulin secretion both in vivo and in vitro [31]. This gene received attention from many research groups following this report, and similar studies were replicated in samples from several populations. Many studies have confirmed the original findings. Substantial association has been confirmed between variants in TCF7L2 and type 2 diabetes among broad ethnic backgrounds, including for example populations of UK [32], Dutch [33], Amish [34], Finnish [35], Swedish [36], French [37], and US [38,39], Indian [40], and Japanese [41] origin. It is noteworthy that, as in the original report, there was clear evidence of a gene dosage effect, such that the 10% of individuals with two copies of the susceptibility allele were at almost twice the risk of developing type 2 diabetes compared to those with only one copy [32,42,43]. Very recently, lack of association between variants in TCF7L2 and type 2 diabetes has been reported in Pima Indians and Chinese diabetics [43,44]. In another association study performed in Arabs [45], the authors reported only a marginal association between rs12255372 and type 2 diabetes risk and no association with rs7903146.

Variants in TCF7L2 have been strongly associated with type 2 diabetes risk [46]. In a Saudi cohort rs12255372 and rs7903146 were not or only weakly associated with T2D. Several studies from non-European ethnic backgrounds have reported a positive association between TCF7L2 variants and T2D. The first, an Indian study, investigated 3 TCF7L2 variants (rs7903146, rs12255372, and rs4506565) and reported significant association between all three SNPs and T2D [40]. In a Japanese study, four TCF7L2 SNPs were explored (rs12255372, rs7903146, rs7901695 and rs11196205) and all four SNPs were found to be significantly associated with T2D, with rs12255372 showing the strongest association [41]. The third study was conducted by Cauchi et al. on Moroccans [46]. Significant association between rs7903146 variant of TCF7L2 and T2D risk in this population was concluded. Additionally, positive association was also reported on Indian Asians [47,48], Pakistanis [49], and Afro-Caribbeans [48]. More recently, a surprising lack of association between TCF7L2 variants and type 2 diabetes was independently reported in two non-European populations including Chinese [43], Pima Indians [44] and in respect to rs7903146 in Emirati Arabs [45]. In a meta analysis conducted by Cauchi et al., the authors reviewed the association of rs7903146 variant with T2D risk by looking at 27 original published association studies (including their own), the authors arrived at a pooled OR of 1.46. There was no overlap between the overall OR and CIs of this meta-analysis and the upper CI of the Saudi cohort (1.27) [50]. However, there is an overlap with three studies included in this meta-analysis [38,48,51]. Therefore, even though significant association was not indicated in the Saudi cohort, a weak association could not be ruled out and justifies a larger replication study in Arabs.

Given the limited studies conducted in Arabs to date, two points are clear. Firstly results indicate differences in Arab populations in relation to genetic risk for T2D. Secondly, data presented in the literature to date clearly demand replication studies, ideally with larger numbers to confirm findings reported thus far. Similarly, further T2D association studies either candidate gene based or genome-wide are warranted in Arabs and may reveal novel risk loci for this important global disease.

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